

been ripening for the change. Clearly the immediate cause of this sudden increase of chemical activity in England was Liebig. His famous school had now been established for several years at Giessen, and if the older men in this country did not altogether put their trust in him, the younger men, breaking through all restraint, flocked from this country to his laboratory, there to become indoctrinated with his enthusiasm for the study of chemistry, and to learn how scientific investigation was to be carried on. At this epoch our Society was founded, and our Journal shows how successful Liebig's teaching was, how a new spirit was instilled into English chemistry, and how much valuable work his students did. Our Society gave them a ready means of publishing their discoveries, and a meeting-place for discussion and mutual interchange of ideas. Thus do I explain the success which from the first has attended on our Society; and having now led you to this point I stop, for my part was merely to speak the prologue, and I leave the story of the development of our Society in other hands.

INFECTIOUS DISEASES, THEIR NATURE, CAUSE, AND MODE OF SPREAD.¹

II.

ONE of the earliest and most important discoveries was that made by Pasteur as to the possibility of attenuating in action an otherwise virulent microbe—that is to say, he succeeded in so growing the microbes, that when introduced into a suitable animal they caused only a mild and transitory illness, which attack, though mild, is nevertheless capable of making this animal resist a second virulent attack. Jenner, by inoculating vaccine, inoculated a mild or attenuated small-pox, and by so doing protected the individual against a virulent small-pox. Pasteur succeeded in producing such an attenuated virus for two infectious diseases—chicken cholera and splenic apoplexy or anthrax; later on also for a third—swine erysipelas. For the first two he produced cultures grown under certain unfavourable conditions, which owing to these conditions lose their virulence, and when inoculated fail to produce the fatal disease, which they would produce if they were grown under normal conditions. What they produce is a transitory mild attack of the disease, but sufficient to protect the animal against a virulent form; thus in anthrax he showed that by growing the *Bacillus anthracis* at a temperature of $42^{\circ}5$ – 43° C. for one week, the bacilli become slightly weakened in action; growing them for a fortnight at that temperature, they become still more weakened, so much so, that if this culture (*première vaccine*) be injected into sheep or cattle (animals very susceptible to anthrax) the effect produced is slight; then injecting the culture which has been growing only eight days at $42^{\circ}5$, the effect is a little more pronounced, but not sufficient to endanger the life of the animal. Such an animal, however, may be regarded as having passed through a slight attack of anthrax, and as being now protected against a second attack, however virulent the material injected. In the case of swine erysipelas, Pasteur found that the microbe of this disease, transmitted through several rabbits successively, yields a material which is capable of producing in the pig a slight attack of swine erysipelas, sufficient to protect the animal against a second attack of the fatal form. Passing the anthrax virus from however virulent a source through the mouse, it becomes attenuated, and is then capable of producing in sheep only a mild form of disease protective against the fatal disorder. Attenuation of the microbes has been brought

about outside the body by growing them under a variety of conditions somewhat unfavourable to the microbe.

Attenuation of the action of the anthrax microbes has been produced by adding to the cultures some slightly obnoxious material (*e.g.* mercuric bichloride 1 : 40,000), by which the growth is somewhat interfered with; or subjecting an otherwise virulent culture for a short time to higher degrees of temperature (anthrax to 56° C. for five minutes; fowl enteritis, twenty minutes, 55° C.); or exposing them for short periods to some obnoxious chemical substance (*e.g.* anthrax to carbolic acid, anthrax to bichloride of mercury 1 : 25,000 for twenty minutes); or the microbes are passed through, *i.e.* are grown in the body of certain species of animals, whereby the microbes become weakened as regards other species (swine erysipelas, anthrax, diphtheria, and tetanus); finally, some microbes become attenuated spontaneously, as it were, by growing them in successive generations outside the animal body, *e.g.* the pneumonia microbe, the erysipelas microbe, and others. However good the nutritive medium, these microbes gradually lose their virulence as cultivation is carried on from subculture to subculture; in diphtheria the culture which was virulent at first loses its virulence as the same culture becomes several weeks old.

All these facts are of considerable importance, inasmuch as they enable us to understand how, in epidemics, the virulence of the microbe gradually wears off and becomes ultimately *nil*, and because they indicate the ways of attenuating microbes for the object of protective inoculations.

Another important step in the study of Bacteria was this: it was shown that they have, besides their special morphological and cultural characters, definite chemical characters. Specific chemical characters (specific ferment actions) of Bacteria have been known for a long time through the earlier researches of Pasteur—*e.g.* the Bacteria causing the acetic acid fermentation of alcohol, the mucoid fermentation, *e.g.* when beer becomes ropy, the lactic acid fermentation of milk-sugar, when milk becomes spontaneously sour, &c.

Similarly, it has been shown that when animal or vegetable matter undergoes the change known as putrefaction or putrid decomposition, substances are produced which resemble alkaloids in many ways, and which, introduced into the circulation of man or animals, act poisonously, the degree of action depending, *ceteris paribus*, on the dose, *i.e.* the amount introduced. These alkaloids—called ptomaines of Selmi—have been carefully investigated and analyzed by Brieger; they are different in nature according to the organism that produces them, and according to the material in which this organism grows: neurin, cadaverin, cholin, &c., are the names given to these substances.

Recent research has shown that pathogenic Bacteria, *i.e.* those associated with, and constituting the cause of specific diseases, are capable of elaborating poisonous substances—toxalbumins or toxins, as they are called—not only in artificial culture media, but also within the human or animal body affected with the particular pathogenic microbe. Thus, in anthrax or splenic apoplexy, Hankin and Sidney Martin have shown this to be the case; in diphtheria (Fraenkel and Brieger), in tetanus (Kitasato), similar toxins have been demonstrated. We can already assert with certainty that a microbe that causes a particular disease causes the whole range of symptoms characterizing the disease by means of a particular poisonous substance or substances it elaborates in and from the tissues of the affected individual.

Another important fact ascertained about some of the toxic substances produced by the different pathogenic Bacteria was this: that if, after they are elaborated in an artificial culture fluid, and, by certain methods of filtration, separated from the Bacteria, and injected into a suitable animal, they are capable of producing the same

¹ Lecture delivered at the Royal Institution on Friday, February 20, 1891, by E. Klein, M.D., F.R.S., Lecturer on Physiology at St. Bartholomew's Hospital Medical School. Continued from p. 419.

disease as their microbes, the rapidity and intensity varying with the amount introduced, so that it became evident that also in the human and animal body the intensity of the particular disease depends, amongst other things, on the amount of poisonous substance elaborated by the Bacteria in the tissues. A further important step made was this: that if the poisonous substance be introduced in such doses that only slight disturbance would follow, and the dose be repeated several times, the body of the animal eventually becomes refractory to the growth and multiplication of the particular Bacteria.

Wooldridge's researches on septicæmia and on anthrax, Roux's researches on septicæmia and diphtheria, Beumer and Peiper, Salmon, and many others, have shown the same for a variety of infectious diseases: in all these instances it has been proved that, when the chemical products of a specific microbe, elaborated in an artificial culture medium or in the animal body, are injected into a healthy animal, this latter is rendered refractory against the specific microbe, so that, if the specific microbe be introduced into such a prepared animal, the microbe cannot grow and multiply, and cannot therefore produce the disease. Pasteur's brilliant researches on protective inoculation against hydrophobia are based on this principle.

The same explanation applies also to those diseases, like scarlet fever, anthrax, fowl cholera, swine fever, certain forms of septicæmia, in which a first, even mild attack is sufficient to protect the animal against a second attack, however large the number and however great the virulence of the particular Bacteria introduced.

For it must be obvious that it is practically the same, whether the protective amount of the toxic substance is produced by the Bacteria in the animal body, as is the case during a mild first attack of the disease, or whether the protective amount of toxin is elaborated outside the body, *i.e.* in an artificial culture, and is then introduced into the animal body. In both instances the effect is the same, *viz.* the animal body is hereby rendered capable of withstanding the growth and multiplication of the particular Bacteria when a new invasion takes place.

What is the cause of this immunity or refractory condition?

In order to explain this, I wish first to draw your attention to the familiar fact that different species of animals, and even different individuals of the same species, offer a different degree of resistance to the different infectious diseases. Whereas splenic fever or anthrax is communicable to man, rodents, and herbivorous animals, it is only with difficulty communicable to carnivorous animals or birds; cholera and typhoid fever are not communicable to any but man; diphtheria is communicable to the human species, to guinea-pigs, cats, and cows, it is not communicable to some other animals; tubercle or consumption is communicable to man and herbivorous animals, in a less degree to carnivorous animals, though these also take it but in a smaller intensity; certain other diseases are common to animals, but are not communicable to the human species.

If we inquire into the cause of this different susceptibility, we find some very striking facts. Take anthrax: cold-blooded animals, *e.g.* frogs, are unsusceptible as long as they are in their natural conditions of temperature; but if a frog be kept at the temperature of a warm-blooded animal, it is found susceptible to anthrax (Pet-ruschki). Birds are not susceptible to anthrax, but if its temperature be lowered a few degrees it becomes susceptible to anthrax (Pasteur).

Or take another instance: rats are not susceptible to anthrax, but if the animals be kept for some time under severe muscular exercise, they become susceptible to the disease. Tame mice are unsusceptible to glanders, but if phlorizin is administered to them for some days, whereby a deposit of sugar takes place in their tissues, they become susceptible to glanders. The susceptibility and

unsusceptibility are expressed by saying that the living tissues in an animal offer in the one case a favourable, in the other an unfavourable, soil for the growth and multiplication of the microbe, and that this unfavourable condition can be altered in a variety of ways, *e.g.* temperature, muscular fatigue, sugar in the tissues, &c. But also a primary favourable condition can be rendered unfavourable: for instance, a human being that has passed through one attack of scarlatina offers tissues unfavourable for the growth of scarlatina microbes; attenuated anthrax protects against virulent anthrax; an animal that has been first treated with repeated small doses of the chemical products of a particular microbe becomes unsusceptible to that microbe.

In order to explain the whole group of phenomena of refractory state, immunity, and protection, a theory has been put forward which is as simple as it is fascinating. There can be truly no greater satisfaction and no greater aim in any branch of science than to express a great number of facts and phenomena by the simplest possible formula; the greatest minds and the most successful philosophers have achieved this. Now, in regard to the numerous and extremely complex phenomena that we have under consideration, a simple formula has been put forward which is supposed to cover all the facts and to explain all the phenomena; this formula is comprised in a single word, "phagocyte." This word is put forth whenever and wherever a difficulty arises in explaining or understanding the complex problems involved in the intimate pathological processes, the refractory condition, the unsusceptibility to and immunity from an infectious disease. To any and every question referring to infectious diseases the answer is simply "phagocyte." By a "phagocyte" is understood one of those elementary microscopic corpuscles abounding in the animal and human body, possessed of spontaneous or amoeboid movement, and occurring in the blood as white blood-cells or leucocytes; in the lymph and lymph glands and most tissues, as lymph corpuscles; in all acute and chronic pathological processes, as pus-cells or round cells. The cells, by their protoplasmic or amoeboid movement, have the power to take up into their interior all manner of minute particles or granules, living or non-living; it seems as if these granules and particles were being swallowed up, eaten, and destroyed by the cells—hence the name of eating globule, or "phagocyte," given to them.

These cells—white blood-cells, lymph-cells, or round cells—are supposed to have the important function to act as the sanitary police against the invading Bacteria, to be always on the look-out for them, and where they meet them to at once engage in battle with them; that is to say, to do as the giants do—to eat their victims. If the phagocytes are victorious—that is, if they succeed in eating up the Bacteria—no harm is done to the animal body; no disease is produced; but if, for one reason or another, the Bacteria succeed in evading the grasp of the phagocyte police, then the Bacteria grow and multiply, and cause the disease. Sometimes this latter result follows on account of the phagocytes not being capable of moving sufficiently briskly to the places of mischief, or, for some inherent reason, not being able to cope with the Bacteria, or being altogether indifferent to the presence of the enemy; when this is the case in an animal or human body, the phagocytes being powerless to destroy the Bacteria, we are supposed to be dealing with a body that is susceptible to the disease; but when the phagocytes do their duty, then the body is unsusceptible to the disease. Again, when an animal or human being, by a mild first attack, or by protective inoculation of one kind or another, becomes unsusceptible to a second attack, this is explained by saying that, though the phagocytes have not done, or have not been able to do, their duty during that first attack, they have now been rendered capable of doing it.

Now, if you ask what is the evidence on which this theory of phagocytosis is based, you will find that it is of the most slender kind, and you will further find that there is an overwhelming number of observations which directly negatives this theory of *universal* phagocytosis, and, moreover, proves conclusively that if phagocytosis has any share in producing a refractory condition on the part of animals towards a particular infectious disease—be that a primary unsusceptibility or an acquired immunity against a second attack—this share is of a remarkably small degree. The whole theory was started by Metschnikoff by the interesting and fundamental observation that, if anthrax bacilli are introduced into the dorsal lymph-sac of the frog—an animal unsusceptible to anthrax while living under normal conditions—the bacilli become inclosed in the lymph-cells, and are gradually broken up; they do not multiply, and do not therefore set up the disease anthrax. This observation, which is easily verified, was the starting-point for the theory. Metschnikoff and others have described similar appearances in other conditions of refractory states. Now the above observation is explained by Metschnikoff in this way: the lymph-cells are acting the part of guardians, swallowing up the bacilli and preventing them from entering the circulation, and thereby preventing the outbreak of the disease. It must seem very extraordinary that this should be really a true explanation of the refractory state of the frog towards anthrax, considering that the bacilli, like other minute particles, when injected into the lymph-sac, would be absorbed and brought into the circulation in a few minutes, nay, seconds—at any rate some hours before the phagocytes have got into the lymph-sac in sufficient numbers to do battle with the bacilli. That the bacilli really enter the circulation in this and other cases, but are destroyed by the blood, not by the leucocytes but by the fluid part of the blood—the plasma—has been abundantly proved; and it has likewise been proved that the fluid part of the blood and of the lymph in general has a remarkable germicidal action, independent of any cellular elements, leucocytes, or other cells. The observation of Metschnikoff admits of an explanation different from that given by him; it may mean, and probably does mean, that the bacilli cannot exist in the fluid of the lymph and of the blood; they are destroyed here, but they take refuge in the leucocytes or lymph-cells in which they can live and exist—for a time, at any rate—these cells offering to them more favourable conditions of existence. In the case of the normal frog, this is also only of a temporary nature, since the substance of the lymph-cells suspended in the lymph or in the blood-plasma becomes likewise permeated with the germicidal influence of the fluid lymph and the fluid plasma, and hence the bacilli soon die, even in the substance of the cells. This explanation is in perfect harmony with the large number of carefully conducted experiments of a host of workers (Fodor, Nutall, Buchner, Petruschki, Lubarsch, and others), according to whom the refractory condition of an animal to a particular infectious disease is due to a chemical germicidal action of the tissue-juices, the lymph, or blood plasma, and independent of any cellular elements. The more pronounced this germicidal action of the juices is, the more refractory the animal. Hence we find that, for instance, when in an animal even a very small number of Bacteria introduced are sufficient to produce disease, the germicidal action of the living blood fluid is very small indeed; but when a considerable number of bacilli are required to produce infection, as in animals possessing only a slight refractory power, this germicidal action of the blood and tissue fluid is greater, and it is greatest of all in those bodies in which not even a large number of bacilli can produce infection, as is the case in animals possessed of immunity. As stated just now, this part of the subject, as to the germicidal action of the fluid of the tissues and the blood, has been worked out very carefully,

and it has been shown that, as regards the destruction of Bacteria, the leucocytes of the lymph and blood, or other similar cells, might just as well be absent altogether. Quite recently the whole argument has been clenched by showing¹ that if an animal susceptible to a particular disease be first infected with the bacilli causing this disease, and then into such an infected animal the cell-free serum or plasma of the blood of an animal refractory to that disease be injected, the development of the disease in the former animal is stopped or prevented. Thus mice are very susceptible to anthrax; if they are infected with anthrax bacilli they die of virulent anthrax within thirty-six to forty-eight hours; but if simultaneously with, or soon after, the introduction of the virulent anthrax bacilli, blood of frog or blood of dog (both animals very refractory to anthrax) be injected into these mice, no fatal anthrax follows. Guinea-pigs, very susceptible to diphtheria, when infected with virulent culture of the diphtheria bacilli, die in the course of a day or two, but rats are little or not at all susceptible to the diphtheria bacilli; and therefore if the guinea-pigs, after infection with the diphtheria bacilli, are injected with rat's blood they recover, this blood being a powerful destroyer of the diphtheria bacilli. Tetanus is easily communicable to mice, in which it produces fatal tetanus in one to three days, but it is not communicable to rabbits; mice infected with the tetanus bacilli and then injected with rabbit's blood do not become affected with tetanus and remain alive.²

While on the one hand, then, the tissue juices and the blood, independent of the cellular elements, possess this germicidal action—small or *nil* in susceptible, larger in animals less susceptible, and largest in unsusceptible animals—there is, on the other hand, a considerable body of evidence to show that the least germicidal action seems to be possessed by those very cells themselves which figure in the theory as the destroyers of Bacteria, as phagocytes; that is to say, that of all the tissues the so-called phagocytes are the materials offering to the Bacteria the best means of existence. Even in cases in which the lymph and blood fluid have against particular Bacteria the greatest germicidal power, the so-called phagocytes are for a time the last refuges for the Bacteria. I will illustrate this by a number of examples both of acute and chronic infectious diseases, as gonorrhoea, Egyptian ophthalmia, Koch's mouse septicæmia, leprosy, and tuberculosis; this latter is particularly instructive, as it demonstrates the absurdity of the alleged phagocytosis of the cells of the spleen in tuberculosis, for it is the latter cells in which the tubercle bacilli thrive well, and which they choose pre-eminently.

[4. Demonstration: tubercle cells and leprosy cells.]

Nay, more than this: non-pathogenic Bacteria cannot exist in the normal blood and in the tissues, in the wall of the alimentary canal, in the tonsils, in the tongue; they are destroyed and are therefore absent in the living tissue. But they can, for a time at any rate, exist in the cells of those parts, and in these, and these only, they are met with; these cells are therefore just the reverse of phagocytes, being the last refuges of the Bacteria.

These facts seem to show that cells containing in their substance living Bacteria is no evidence whatever of a battle going on between the cells and the Bacteria, but rather the reverse. The assumption of the presence in the so-called phagocytes and similar cells of a "defensive proteid" seems therefore opposed by these facts. The cells seem to possess a particular chemical attraction for the Bacteria, just as is possessed by certain chemical substances; such attraction is spoken of as *positive chemotaxis* in contradistinction to *negative chemotaxis*—that is, the opposite or repulsive interaction between

¹ Ogata and Tasuhara, *Mitth. der Med. Facultät d. Kais. Japan Universität, Tokio*.

² Behring and Kitisato, *Deutsche Med. Woch.*, 1890, N. 49.

Bacteria and certain substances. This line of inquiry is of quite recent date, and promises to produce important and interesting results.

From all this we conclude, then, that in some cases the blood and tissues are, or include, a natural antidote; in others the antidote is not present naturally, and is only furnished by the Bacteria themselves, and still in others the tissues, though possessed of this antidote, may lose it owing to altered conditions.

Another point worth considering is the peculiar inimical action exerted by one microbe on the other: this practically means that the products of one microbe either prevent the growth of another microbe or neutralize its toxic action. It is perfectly well established that while the products of one microbe exert an inimical action, when present in sufficient amount, on the growth and life of the same microbe (the protective inoculation by chemical products of the Bacteria cited above), the accumulation of the products of the particular microbe interferes with, and eventually altogether stops the further growth of its microbe. Outside the body this is easily proved in artificial cultivations. Inside the body it is proved by those cases in which recovery takes place.

It has been shown that while some pathogenic microbes can well thrive side by side in the same culture, inside or outside the body, there are others where the growth of one is antagonistic to the action of the other: erysipelas and anthrax (*v. Emmerich*), swine erysipelas and swine fever, anthrax and *Bacillus pyocyaneus* (*Charrin*), anthrax and *Staphylococcus aureus*; this is due to the fact that the chemical products of one species inhibit or neutralize the other species. That this antagonism is really of a chemical nature is shown in the case of anthrax and *Bacillus pyocyaneus*; if the chemical products of this latter microbe be injected into the animal simultaneously or soon after inoculation with the anthrax bacilli, no anthrax disease ensues, the anthrax bacilli do not multiply and do not produce the disease. Apart from specific antiseptics, there exist, then, in the battle against the action of pathogenic microbes which have already entered the system of an animal, the following means: (1) the chemical antagonism offered by the healthy tissues themselves—in some cases this is nought, in others very great and powerful, alterable by various conditions; (2) the germicidal action of the blood and tissue juices of unsusceptible animals on the multiplication of pathogenic Bacteria within a susceptible animal; (3) the antagonism existing between the Bacteria and their own chemical products; (4) the antagonism of one species and its chemical products against another species. These principles have, then, to be borne in mind as indicating the ways in which the microbes can be prevented from producing eventually the disease in a body into which they have found access. Pasteur's hydrophobia inoculations, and many of the recently published results of curative inoculations against tetanus, against anthrax, and against diphtheria, are illustrations of these principles.

The principle on which Koch's antituberculous lymph acts is apparently of a different nature. Koch has found by experiment on guinea-pigs that if the chemical products or an extract of the substance of the tubercle bacilli be injected into a body affected with tuberculosis, the tubercular tissue becomes necrotic, while the tubercle bacilli themselves remain unaffected; at the same time a remarkable reactive inflammation sets in, by which the necrotic tissue becomes eliminated, either spontaneously, *e.g.* where the tubercular process is superficial, as in lupus of the skin, or it may be removed by surgical aid, as in tuberculosis of the bones and joints. All who have followed the numerous cases treated in this manner must agree that it is an immense advance on all previous methods of treatment of some forms of lupus and of bone tuberculosis.

After having shown you what an enormous amount of

accurate knowledge about the nature and causation, about the prevention and treatment of infectious diseases has been gained by the experimental method and by this alone, it will hardly be credited that a number of persons, as well-meaning as they are ill-instructed, are still maintaining the contrary; it is they who have succeeded in inducing Parliament to pass a law restricting, if not in some cases altogether prohibiting, the use of that method. This law is interfering with research in this country to a large extent, and has even put a stigma on those who are engaged in elucidating truths that are for the benefit of mankind, and of the animals themselves: what can be of greater benefit in the battle against diseases than the knowledge of their causes, and the devising of means for their prevention and treatment?

Fortunately for progress in general, this country is the only one in which such restrictions disfigure the statute-book; other countries, more enlightened and able to recognize the value of researches of this kind, have wisely resisted the clamour for restrictions.

In connection with all this knowledge, of which I have only been able to give you an outline, I have heard it stated that "ignorance" (meaning the ignorance of former times) "is bliss" as compared with the present knowledge of the dangers surrounding us; but I have also heard it stated that the wise man, knowing and recognizing the nature of these dangers, has the possibility given him of avoiding and preventing them, and no truer words have been spoken than these, that "he who cures a disease may be the skilfullest, but he that prevents it is the safest, physician."

My best thanks are due to my friend Mr. Andrew Pringle for the admirable photographs prepared by him of the microscopic slides illustrating the different pathogenic microbes exhibited, and to my friend and pupil Mr. Bousfield for the fine lantern slides of tube cultivations.

THE ROYAL METEOROLOGICAL SOCIETY'S EXHIBITION.

THE twelfth annual Exhibition of the Royal Meteorological Society was opened on Tuesday evening, March 3, in the rooms of the Institution of Civil Engineers, 24 and 25 Great George Street, Westminster. This year's Exhibition is devoted to rain-gauges and evaporation-gauges, and also such new instruments as have been constructed since the last Exhibition. It might at first be thought that an exhibition of rain-gauges would be a very small and insignificant affair, and would not be of any interest to the general public. Anyone, however, visiting the Exhibition will at once see that a very large collection of various forms of rain-gauges has been got together by the Society, and that the information obtained from the records of these simple instruments is of the highest importance. There are altogether fifty-six different forms of rain-gauges shown in the Exhibition, and it is interesting to compare the old with the new patterns.

Side-tube rain-gauges of various diameters are exhibited. In this instrument the water passes into the body of the gauge, and also into a glass tube in the front, and stands at the same level in each. As the combined area of these tubes is very much less than that of the receiving surface, the natural depth of the rain is proportionally increased, and thus the scale is lengthened in proportion—usually about eight or ten times—so that the quantity can be read off to hundredths of an inch. The objection to this form of instrument is that the glass tube is liable to be burst by frost, and the record lost.

Messrs. Negretti and Zambra exhibit a contracted float-gauge, the receiver of which contains a copper float, to the upper side of which a rod is attached. When rain falls, the rod is lifted, and, owing to the small area of the